



## NOVEL TBX19 MUTATION AS CAUSE OF HYPOGLICEMIA IN TWO SIBLINGS

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We describe a female neonate born from consanguineous parents who presented at birth with respiratory distress and severe hypoglycemia. At six months of age, the child was admitted to the Intensive care Unit because of sepsis. Blood tests showed severe hypoglycemia (19 mg/dl), hyponatremia (Na 132 mmol/l), compensated metabolic acidosis and increased inflammatory markers. During the hypoglycemia episode, endocrine analyses revealed low levels of ACTH (<5 pg/ml), cortisol (<1 mcg/dl) and basal GH (2.22 ng/ml), but normal thyroid hormones. The magnetic resonance imaging of brain and of the pituitary gland showed normal morphology. After diagnosis of **central hypocortisolism** we immediately started her on substitution therapy with hydrocortisone. At 14 months of life she was started on GH therapy for decreased growth velocity and low GH levels in response to Arginine test.

Fig. 1: genealogic tree of this family.

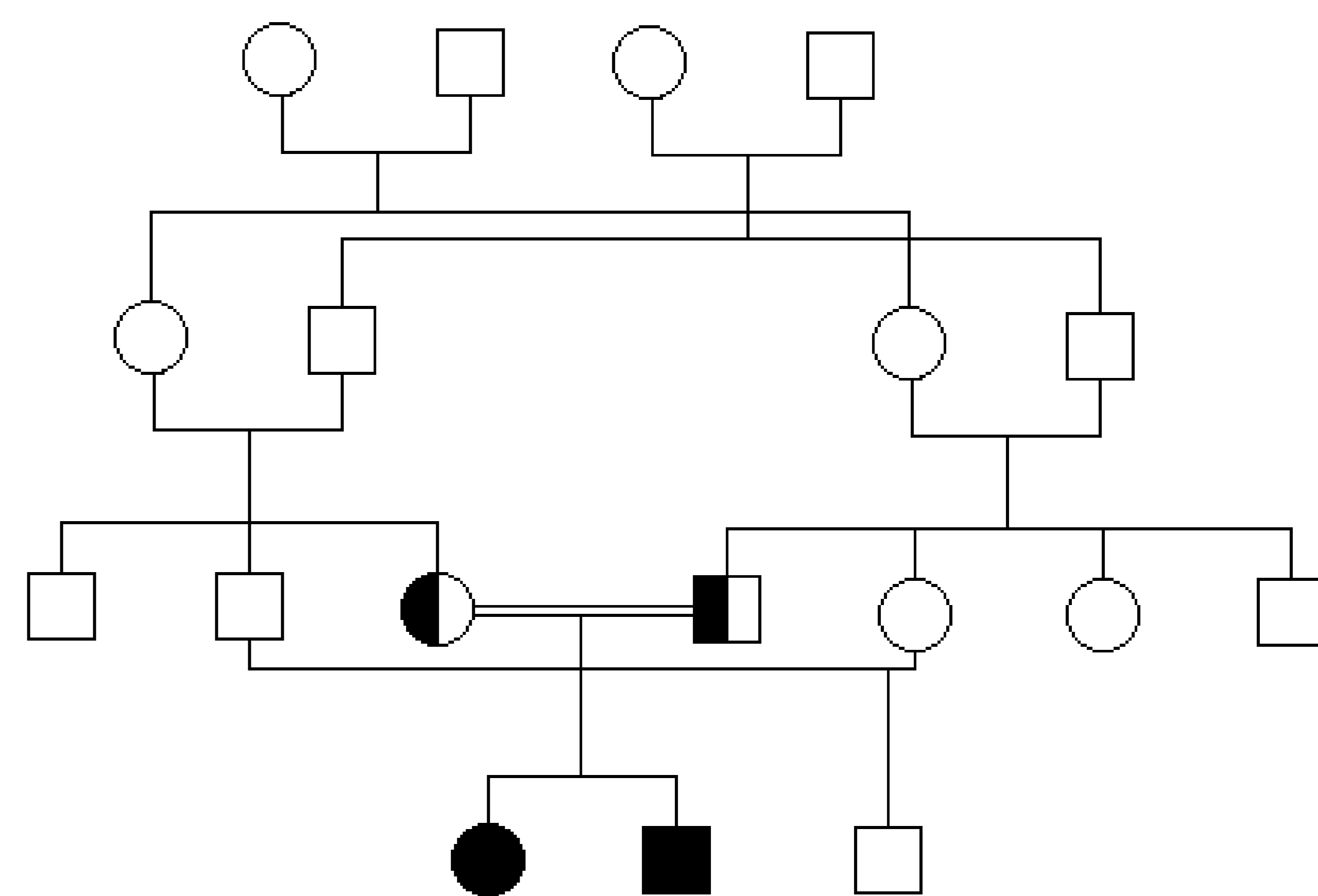
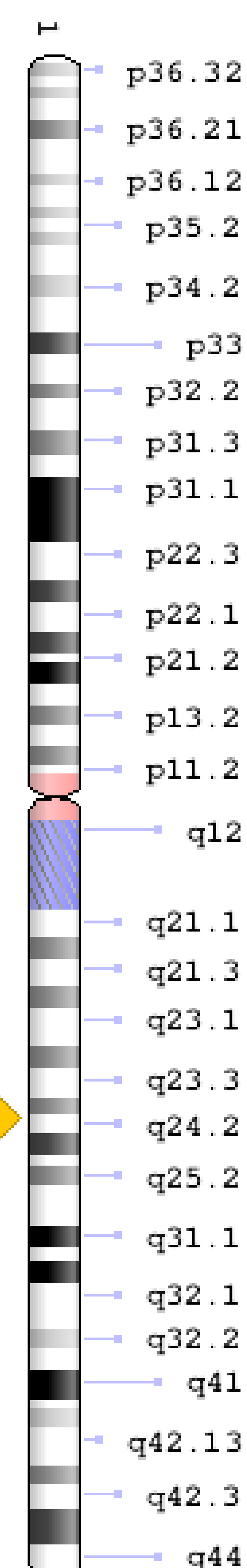


Fig. 2: cytogenetic location of TBX19 gene in 1q24.2, which is the long (q) arm of chromosome 1 at position 24.2.



After two years, a second child was born in the same family (Fig.1): he presented at three hours of life with profuse sweating, severe hypoglycemia and persistent vomiting. Because of the family history, we performed blood tests which revealed isolated **central hypocortisolism** (ACTH <5 pg/ml, serum cortisol <1 mcg/dl), while basal GH, thyroid hormone levels and magnetic resonance imaging of brain and pituitary gland were normal. We started him on substitutive therapy with hydrocortisone with quick improvement of his clinical condition.

Genetic analysis of the two siblings by using a specially constructed NGS panel revealed a **novel homozygous mutation of TBX19 gene (c.269 T> C (Leu> Pro) of exon 2)** in both of them and as heterozygous in their parent (Fig.2). Biallelic mutations of this gene are **associated with congenital ACTH deficiency**. This mutation, not previously described, affects a highly conserved region of the protein, and was reported as probably damaging suggesting that is most likely causative of the central hypocortisolism described in the two brothers.